

**APPLICATION FOR UNITED STATES PATENT**

**TREATMENT OF AGE-RELATED MACULAR DEGENERATION**

**S P E C I F I C A T I O N**

**Background of the Invention**

This invention concerns treatment of wet age-related macular degeneration (AMD) in the eye, and in particular concerns use of radiation to treat such macular degeneration, the radiation being administered from behind the sclera. Treatment of ocular tumors also forms a part of the invention.

Wet age-related macular degeneration has been the leading cause of blindness in the United States, and a leading cause in the world. It is characterized by the growth of abnormal blood vessels from the choroidal membrane at the back of the eye, in the macular area of the retina including the fovea and immediately surrounding regions. This is called "choroidal neovascularization" (CNV). The term "wet" refers to the fact that these abnormal blood vessels leak and damage the macula, causing central vision distortion. Thus, the highest resolution vision of the patient is severely compromised or lost.

Approximately ten percent of AMD cases comprise wet AMD, and

this is the type which can lead to blindness. Dry AMD comprises approximately ninety percent of AMD cases, but a certain percentage of these (approximately ten percent) eventually progress to wet AMD.

Of wet AMD patients, approximately seventy percent of these cases are classic wet AMD, while approximately thirty percent are what is known as occult AMD. In both cases CNV occurs, invading the choroid and the space above the choroid with proliferating blood vessels which cause damage. In the case of classic AMD, the new blood vessels remain essentially intact, while in occult AMD the blood vessels leak, form a somewhat amorphous mass, and obscure the ability of a physician to see the vessel through an ophthalmoscope. Thus, any treatment aimed specifically at these vessels, requiring visual identification and location of the vessels, fails for occult AMD.

There have been several approaches to treatment of wet AMD. In both photodynamic therapy (PDT) and transpupillary thermal therapy (TTT) laser beams are used, directed through the front of the eye. These have had varying degrees of effectiveness, with PDT generally being the more effective of the two. In PDT, the treatment consists of administering photosensitizing dye followed by laser treatment, which sensitizes the dye to affect the CNV condition. Results of both TTT and PDT have been less than ideal. With PDT, based on one study, only 15% of AMD

patients would meet the Macular Photocoagulation Study Group (MPSG) guidelines for treatment; thus, most AMD patients would not benefit from this treatment. In addition, the cost for this treatment has been extremely high and its cost-effectiveness is in question.

It is also noted that although the FDA recommends PDT treatment of patients with predominantly classic choroidal neovascular lesions from AMD, in most cases neovascularization recurred within three months. Thus, patients will probably need three to four treatments per year for this therapy to be effective, and the treatment basically preserves vision rather than improves visual acuity.

Researchers have discovered that x-ray radiation can be effective in treating CNV. Radiation has been administered from external sources, through the temple area, and also via brachytherapy using "plaques" which support radioisotope pellets, these plaques being implanted onto the back side of the eye, against the sclera, by insertion around the exterior of the sclera. These implanted plaques have been left in position for a prescribed duration of time, e.g. about 30 hours, or a range of about 18 to 65 hours at 17.6 Gy. Results of one study showed stabilization or sight improvement in about 45% of treated patients. After a seven year follow up, no sight-limiting radiation complications were noted in any patients. Thus, x-ray

radiation, particularly administered by brachytherapy, is known to have some efficacy in the stabilization and improvement of the CNV condition of macular degeneration.

Patent No. 6,443,881, issued to Paul Finger, describes use of these plaques and methods for locating the plaques using light sources mounted on the plaques.

External beam treatment is difficult and generally limited to highly specialized practitioners, with capital cost for equipment very high. This treatment is difficult for several reasons, including inability to produce a very small beam specific to the target, location of the beam precisely on the target, radiation damage to other structures, including brain tissue, and avoidance of the optic nerve and radiation retinopathy.

In addition to other limitations discussed above, the use of isotopes is not ideal. They are extremely limited as to choices of specific activity of the isotopes, as well as energy.

Further, the isotopes must be shielded during emplacement for brachytherapy, as well as shielded directionally to protect adjacent structures, since the isotopes are isotropic emitters.

A much improved treatment for CNV of macular degeneration would be a controllable x-ray source which can be placed non-surgically adjacent to the macula, with accurate placement, with reliably accurate directional emission, and which can be

controlled as to depth of radiation penetration as well as dose.

These are objects of the present invention described below.

#### Summary of the Invention

This invention is a method and device by which a miniature x-ray source is inserted around the globe of the eye, non-surgically, to locate the source directly adjacent to the macula, behind the eye and against the sclera. The miniature x-ray tube is switchable off/on as well as controllable, in preferred embodiments, as to voltage (penetration) and current (dose).

Insertion of the source is via a catheter/probe which is inserted around the globe to the back of the eye and positioned adjacent to the target tissue. The miniature x-ray tube within the catheter is on the order of about 1 mm in diameter with a length of approximately 7 mm (although dimensions can vary). By this device, a therapeutic dose of ionizing radiation is delivered to the abnormal vessels in the choroid layer. This therapeutic radiation tends to seal or close the bleeding vessels through a process that causes vessel fibrosis. Adjacent tissue cells which are not actively proliferating are less affected by the radiation, as is well known.

An important advantage of delivering ionizing radiation from the back of the eye is that a therapeutic dose can be given to the lesion without damaging structures of the eye, i.e. the lens,

retina and optic nerve. The membranes at the back of the eye are relatively radioresistant.

The invention encompasses a method and means for accurate location of the catheter and x-ray tube behind the eye. Several different guidance techniques can be used. In accordance with one technique a bump or ridge is provided on the probe or on the guide, forming a moving mound on the retina, as the device is manipulated, visible to the physician from the front of the eye. This provides a fiducial for the physician to accurately locate the anode end of the x-ray tube. Another approach is using light or invisible radiation, directed from the front of the eye, as a tool to locate the probe either spatially or temporally. As one example, a light emitting device from the front of the eye can generate a series of expanding rings of light. These can be sensed by a plurality of sensors on the exterior of the probe, the tissues from the retina to the back of the sclera being relatively translucent. Even though the rings of light will be somewhat scattered when reaching these sensors, their peaks can be detected and this will give enough information, fed back to the console, to determine which direction the probe should be moved to effectively center the device and align the radiation source to the macula.

Infrared radiation can be used advantageously in location of the probe. IR can be directed in from the front of the eye,

invisible to the patient and thus not uncomfortable to the patient, and this radiation will penetrate through the retina, choroid and sclera to the sensors on the device.

Another alignment device can have light sources positioned on the probe itself, as in the Finger patent referenced above. By the invention these light sources can be cleaved optical fibers or polished fibers with redirecting reflectors at the fiber ends (microprisms), with the origin of the light being back in the console. These fiber ends can serve as "headlights" to locate the probe by reference to the position of the light sources as they appear from the front of the eye. Other variations can include color gradations shone through the front of the eye, a grid of light patterns, or other devices involving the sensing of light from either the probe or from the front of the eye. A modified embodiment to use fluorescence of a material struck by the x-rays to enable seeing the location of the x-ray beam by looking into the front of the eye. A fluorescence material could be put into the blood or the ocular fluid to fluoresce with short bursts of x-ray radiation to locate the device. Alternatively, the tube itself can have a fluorescing material, to glow when excited by x-rays and visually locate the probe.

With the invention the radiation dose and depth can be matched to the prescription for the CNV condition, while

minimizing radiation to healthy adjacent structures. Several parameters are adjustable to achieve this. In addition, the x-ray tube in the probe preferably is made directional, and an ideal window of radiation can be provided for the treatment as desired, relative to the distance of the treatment area and the width of the treatment area as seen from the x-ray tube.

Filtration of the x-ray beam from the miniature tube can be put in place if needed. This can greatly reduce low-energy emissions (i.e. "hardening" the beam), thus reducing dose in the near field, i.e. the sclera, where radiation is not desired.

This in combination with standoff of the source after placement and adjustment of voltage, enable optimizing dose to the choroid, sclera and retina.

It is important that the probe be immobilized during treatment. Several methods can be used. The "bump" on the probe device described above can be inflatable, thus being inserted flattened but inflated (with liquid) when near the macula. Further inflation can help hold the probe against the adjacent tissues (and also stands the source off from the tissue as described below). Another inflatable balloon can be at the back side of the probe, and a further balloon(s) can be located on the catheter proximal to the x-ray source for further immobilization of the catheter and probe.

Another aspect of the invention is that drugs can be used to

enhance the effectiveness of the radiation treatment, thus allowing lower radiation doses to be administered. Similar to the concept of PDT described above, radiation-enhancing drugs can be administered systemically, causing the irradiated regions to be more sensitive to radiation, but having no effect on the body tissues in non-irradiated areas.

It is therefore among the objects of the invention to improve radiation therapy as a treatment for wet exudive macular degeneration, by use of a probe having a controllable radiation source which can be accurately located behind the macula for accurate delivery of the radiation. These and other objects, advantages and features of the invention will be understood from the following description of preferred embodiments, considered along with the drawings.

#### Description of the Drawings

Fig. 1 is a schematic view in sectional plan showing an eye and a catheter being inserted non-surgically around the globe, behind the macular region.

Fig. 2 is an enlarged view in sectional plan showing the catheter or probe of the invention behind the macular region.

Fig. 3 is a schematic partial plan view showing an embodiment of the catheter of the invention having one type of x-ray source locating means, in this case a protrusion on the

surface of the catheter, which also serves as an immobilizer and a standoff to improve radiation surface to depth ratio.

Fig. 3A is a view similar to Fig. 3, showing an inflatable protrusion on the catheter or probe, and also showing additional inflatable balloon devices for immobilization.

Fig. 4 is a schematic view as seen from the front of the eye and showing the macula and surrounding blood vessels and also revealing the x-ray source of the invention positioned behind the macula (which would actually not be visible through the eye), in this case showing incorrect positioning of the x-ray source.

Fig. 5 is a view similar to Fig. 4, but showing the x-ray source correctly positioned behind the macula.

Fig. 6 is a schematic view showing expanding rings of light shone in from the front of the eye, as another method and device for properly locating the x-ray source behind the macula.

Fig. 7 is a schematic view showing a grid of light lines which can be sequentially activated and detected from sensors on the probe or catheter device, as another means and method for properly locating the x-ray source.

Fig. 8 is a schematic view indicating light sources mounted on the catheter or probe device as another alternative for properly locating the x-ray source behind the macula.

Fig. 9 is a schematic view showing, in a primarily plan view, a limited radiation pattern emitted from the x-ray source

and treating the choroid layer behind the macula.

Fig. 10 is a schematic plan sectional view showing an x-ray tube for side-looking, directional radiation.

Fig. 11 is a schematic sectional view showing "keying" of an x-ray source within a surrounding sheath containing cooling channels.

Fig. 12 is a sectional schematic view showing tangential or chordal radiation with respect to the globe of the eye, from the x-ray source toward the macula.

Fig. 13 is a graph of dose versus depth of penetration of radiation, i.e. a dose profile for one embodiment of the system in method of the invention.

#### Description of Preferred Embodiments

Fig. 1 of the drawings shows a patient's eye 10, generally in plan view and cross section, and schematically indicates a probe or catheter device 12 inserted around the globe of the eye, along the surface of the sclera 14. The macula, or macular region, is shown at 16, a region of the retina of the eye. The probe or catheter device 12, which is shown schematically and may include an outer sheath or guide within which the catheter is inserted, includes a switchable x-ray source 20 at its distal end. The source 20 preferably comprises an x-ray tube which emits radiation when switched on and which optionally can be

varied as to current and voltage, emitting a side-looking directional radiation toward the macula 16, through the sclera 14 and the choroidal membrane or layer immediately behind the macula. Accurate positioning of the x-ray source 20 is an important aspect of the invention and is discussed below.

Fig. 2 is an enlarged, detailed view, schematic in its illustration of the x-ray source 20. The source 20 is immediately behind the sclera 14, and the source, or the sheath or guide surrounding the source, directly contacts the back surface of the sclera. As the drawing schematically indicates, the choroid, or choroidal layer 22, is the next tissue layer in from the sclera. The sclera may be about 1 mm in thickness in this region, while the choroidal layer may be only about 0.5 mm thick. Immediately inside the choroidal layer is the retina 26.

The fovea 28 is at the center of the macular region 30, which is typically considered as a region of about 5 to 6 mm in diameter around the phobia (including the foveola, fovea, parafoveal and perifoveal regions). As Fig. 2 indicates, this region is very close to the optic nerve 32, where radiation is to be avoided. The choroidal layer 22, as explained above, is the region where CNV of age related macula degeneration occurs, and this is the layer, directly behind the macula, to be treated with x-ray radiation according to the invention.

Figs. 3-8 are concerned with properly locating the probe or catheter 12, and particularly the x-ray radiation, behind the macula. In Fig. 3 one scheme is illustrated for indicating to the physician the location of the x-ray tube behind the retina, and thus allowing adjustment and proper positioning of the probe to approximately center the tube behind the macula. By this arrangement the probe 12 containing the x-ray tube 20, i.e. the exterior of the apparatus inserted around the globe of the eye (which can be a guide), has a "bump" or protrusion 32. This protrusion 32 which can be considered as exaggerated in relative size in Fig. 3, forms a moving ridge or bump in the retina, which is visible to the physician using an optical instrument from the front of the eye. As seen in the schematic view of Fig. 3, the bump 32 preferably is centered over the anode of the x-ray tube 20, i.e. the portion of the tube from which the x-rays 34 originate. In Fig. 3 the end of the probe 12 is shown as round, in atraumatic type 36.

Fig. 3A shows a variation of what is shown in Fig. 3. In both Figs. 3 and 3A, the bump 32 or 32a forms an immobilizing function as well as the locating function described above. The bump 32, 32a pushes against the sclera and thus tends to wedge the probe device more tightly between the sclera and adjacent tissue. Further, this bump 32, 32a serves to stand the radiation source 20 off from the sclera and choroid layers, thus improving

surface to depth ratio for the emitted radiation. In Fig. 3A the bump 32a is inflatable, via a lumen (not shown) in the catheter 12a, and the amount of inflation can be varied as needed. This standoff distance is correlated with the voltage setting for the tube 20, thus enabling the physician to optimize x-ray radiation dose in the choroid while minimizing dose in the retina and in the sclera. Fig. 3 also shows an additional inflatable balloon protrusion 33 which can be located on the opposite side of the probe device from the radiation side. This balloon 33, also inflatable via a lumen or duct (not shown) in the catheter 12a, like the bump 32a, is deflated when the probe is inserted. It can be inflated to a selected inflation for helping immobilize the probe after the tube has been properly located behind the macula. Also shown in Fig. 3A is a third inflatable balloon structure 35 which can be included at a selected location along the length of the catheter 12a, to further immobilize the probe and to isolate the catheter tip and x-ray source from movements of the catheter at the proximal and after properly locating the probe. Again, the balloon 35 is deflated during insertion.

Vacuum, i.e. suction against tissues, can also be used to immobilize the device after it is properly located. Suction can be applied through a separate lumen (not shown) in the catheter, and can be applied via openings on the protrusion 32a or 33, spreading the suction over a relatively wide area.

Figs. 4 and 5 show schematically, relative to the procedure of properly locating the x-ray tube 20 behind the macula (it actually would not be visible from the front of the eye). Fig. 4 shows an example of incorrect positioning of the probe. Blood vessels to the macular region are indicated at 38 in this drawing.

Fig. 5 is similar to Fig. 4, but shows the probe 12 and x-ray tube 20 correctly positioned behind the macula 30. Figs. 6, 7 and 8 show examples of optical methods and means by which this can be achieved.

In Fig. 6 is shown a series of light rings 40, 42, 44 and 46. These are directed in from the front of the eye, centered on the macular region which is shown at 30 in Fig. 6. The centering of the rings is done by the physician, using an instrument at the front of the eye. The light rings, 40, 42, etc. are constantly expanding (and reappearing at center). Behind the retina is the probe, with a plurality of sensors 48 (in this case four) mounted on the device and preferably centered around the x-ray emission point of origin. These sensors 48 detect the passing of each ring of light 40, 42, 44 and 46 as it expands. Even though the light rings will be considerably scattered as they pass through the partially translucent retina, choroid and sclera to reach the sensors 48, their peak intensities will be detectable at each point 48. Thus, as the rings expand the timing of each peak

detection by each of the sensor points 48 is fed to a console (not shown) connected to the probe instrument, and from this information the location of the sensors relative to the center point of origin of the light rings can be determined. When centered the detectors 48 will all detect light peaks simultaneously. Thus, an instruction can be generated to the physician as to what direction the probe should be moved in order to achieve correct positioning, or the position of the probe relative to the macula can actually be displayed on a screen on or connected to the console. A robotic device can be used to position the probe, with robotic feedback from the sensors 48 and console.

Fig. 7 shows another probe-location method and system. By this method, a grid of light lines, e.g. vertical light lines 50 and horizontal light lines 52, are generated by an instrument which directs the light in from the front of the eye. The four sensor points 48 discussed with respect to Fig. 6 are shown behind the grid of lines. Fig. 7 is only schematic, and the line spacing in the grid is sufficiently small that light from at least one light line will always be detected by at least some of the plurality of sensors 48 mounted on the probe device. As discussed above, this light will be highly scattered after passing through the retina, choroid and sclera, but its peaks will be detectable. The grid of lines 50, 52 is located by the

physician as accurately as possible relative to the macula of the eye, as by a special, distinctively illuminated location intersection 54. The light lines can be sequentially activated, so that the feedback from the sensors 48 will always identify which line of light was detected and by which sensor or sensors. This will give enough information to tell the physician (or a robotic probe manipulator) where the probe is located, and which direction and how far to move it in order to make it properly located behind the macula.

Alternatively, the grid shown in Fig. 7 can represent scanned light lines moving across the retina (fewer lines are needed). By temporal synchronization, the location of each light line at any time is known, allowing the sensors and connected logic to locate the probe. Note that only two, or even one sensor 48 is sufficient for this form of scan locator.

Fig. 8 shows another scheme for properly locating the x-ray tube 20 behind the macular region 30. This arrangement is somewhat similar to that of the Finger patent discussed above, in that light sources 56 are mounted directly on the probe. Four are shown in Fig. 8. In the invention, however, these light sources are angularly cleaved optical fiber ends which receive light from an illumination source in the console. The fiber ends 56 are sufficiently bright that the physician can see the pattern of these light sources behind the macula, and can locate the

probe accordingly. The fiber ends may be angularly cleared, or polished and redirected by reflectors (microprisms).

Another method for indicating and confirming position of the x-ray source behind the eye is to provide a means of seeing the x-ray radiation itself, or seeing evidence of the x-ray radiation, by looking into the front of the eye. This method could involve fluorescence, of a casing around the x-ray source, or of a medically acceptable substance put into the blood stream, which substance fluoresces when absorbing x-ray radiation. Such a substance could be injected into the intraocular space.

Another way of producing a fluorescing indicator is to use the x-ray tube itself or a transmissive plate or coating on the x-ray tube, as a substance which will fluoresce when struck by x-rays. The applicant has found that sintered aluminum nitride will fluoresce when excited by x-ray radiation.

The x-ray therapy of the invention can be used in conjunction with photodynamic therapy, as mentioned above. By using the two therapies simultaneously (or closely in time to one another), the disruption caused by PDT can be synergistically complemented by radiation therapy. PDT essentially causes a disruption of the capillaries of the choroid layer by a photoactive chemical substance as explained in Patent No. 6,548,542 (col. 4, l. 61 - col. 5, l. 4), incorporated herein by reference. The photo-activated substance is thought to break

down cellular structures and other effects as noted in the '542 patent, resulting in occlusion of the CNV rasculative. X-ray radiation delivered in conjunction with PDT can help remediate AMD in two ways: first, the direct effect is to disable rapidly dividing cells, thus reducing the population of cells which can cause the problem by growing new inappropriate vessels (CNV), and secondarily, the radiation assists in the effects of the PDT by preventing the repair response which naturally follows the PDT treatment.

The invention also encompasses use of radiosensitizing substances in the blood vessels to enhance their sensitivity to radiation. This is the subject of copending application serial No. 09/851,372, filed May 7, 2001, assigned to the assignee of the present invention. That copending application is directed primarily at a combination of radiation and radiosensitizer delivery devices to inhibit hyperplasia following balloon angioplasty. The application discloses radiosensitizers such as taxol, misonidazole, metronidazole, etanidazole, 5-fluorouracil, texaphyrin, C225 (an anti-EGFR monoclonal antibody), and cyclooxygenase-2 inhibitor. In the present invention, a radiosensitizer such as one of these substances is put into the blood in an effective amount to sensitize the cells in the choroid layer such that a lower dose of x-ray radiation via the probe of the invention can be administered.

Fig. 9 is a simple schematic showing the x-ray source 20 at the distal end of the catheter or probe 12 and properly located behind the macular region 30 of the eye. The portion of the choroidal layer 22 to be irradiated, i.e. the choroid directly behind the macula, is indicated at 60. The x-ray radiation is shown in a diverging pattern at 34, emanating from a source (the anode) 62 in the x-ray tube, at the proper angle to irradiate the region of interest 60 in the choroid. Fig. 9 shows adjacent structures are irradiated, including the sclera 14 and the retina 26. An approximate dose to depth curve is shown in Fig. 13. The sclera necessarily receives more radiation than the other structures, but the sclera comprises relatively quiescent cells which are not rapidly proliferating, and the radiation dose is not so excessive to cause a problem. The next layer is the choroid with the CNV condition of macular degeneration. This region receives sufficient radiation to provide therapeutic benefit to the patient. Beyond the choroid 22 is the retina 26, which receives a still smaller dose. Regions deeper toward the front of the eye, including the lens and cornea (not shown), receive progressively less dose. With proper selection of voltage filtering and stand-off the switchable x-ray source can deliver considerably less radiation to structures distal to the target tissue (choroid) than current isotope plaque treatment. No radiation damage has been seen in patients treated with

plaques with up to 7 years follow-up.

Fig. 10 schematically indicates an anode construction for the x-ray tube 20, for achieving side-looking, directional emission. In this arrangement the anode comprises an angled face 64, i.e. at approximately  $45^\circ$  (from  $22^\circ$  to  $60^\circ$ ) to the direction of the approaching electron beam 66, so that emission is essentially through an arc A. However, the x-ray tube 20 is shielded, as shown at 68 on the back side and 70 on the front side, so that only a desired window of side-looking radiation is emitted, through a desired angle B. The arc of radiation is limited in two dimensions, thus producing radiation which can be an approximate cone. The geometry of the tube and its shielding are selected so that, with the distance from the anode to the choroid layer known, and the width or diameter of the choroid behind the macula known, the correct angle of radiation is emitted. Shielding alone can be relied on to produce the side-looking radiation desired from an x-ray source without an angled anode.

Fig. 11 is a simplified schematic view showing a "keyed" arrangement for proper rotational orientation of the x-ray source within the catheter or an immediately surrounding sheath 72. The x-ray tube or source 20 has a ridge or protrusion 74, which fits within a complementary channel 76 within the sheath 72 or probe. In the case illustrated, the immediately surrounding structure is

a sheath 72 having cooling channels 78, 80, etc. This may be surrounded by a guide 82 shown in dashed lines, and the sheath 72 itself may be keyed for proper rotational orientation within the guide 82. A keyhole shape such as illustrated with the tube 20 is not needed; a simple, small elongated ridge or a shorter bump, or a non-round shape such as elliptical will suffice to provide orientation. It is imperative that the side-looking x-ray device be properly oriented to direct the radiation toward the choroid region to be treated. This can be achieved by many different arrangements.

Fig. 12 shows an alternative method for irradiating the CNV affected choroid region, shown at 84 in this simple schematic. The optic nerve 32 is shown in Fig. 12 but is behind the plane of treatment in which are located the probe 12 and the treatment region 84. In this case the x-rays 86 are directed generally tangentially to the eye, or chordally, as illustrated. This is a method for avoiding any significant radiation to the retina, indicated at 26, by passing the radiation essentially tangentially or chordally through the sclera and a part of the choroid, to the region of CNV directly behind the macula. The x-ray source tailored to produce a flat beam of the appropriate width and direction. Distances in Fig. 12 are neither to scale nor proportional.

The apparatus and method of the invention also can be used

to treat ocular tumors with radiation. The same catheter is used, with a switchable source having an appropriate direction of radiation, for tumors at different locations in the ocular tissue.

The above described preferred embodiments are intended to illustrate the principles of the invention, but not to limit its scope. Other embodiments and variations to this preferred embodiment will be apparent to those skilled in the art and may be made without departing from the spirit and scope of the invention as defined in the following claims.

WE CLAIM: